Primerjava med vzroki za umrljivost dojenčkov in cepljenjem med rednim programom cepljenja v Sloveniji

Correlations between infant mortality and recommended immunization schedules against vaccine–preventable diseases in Slovenia

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Izvleček

Namen: *Umrljivost dojenčkov je pomemben kazalnik kakovosti zdravja ter gospodarskega in družbenega okolja celotnega prebivalstva. V Sloveniji je v zadnjih 55–ih letih smrtnost dojenčkov izredno upadla in cepljenje proti nalezljivim boleznim je zagotovo eden od pomembnih dejavnikov. V skladu s programom cepljenja so v prvem letu starosti dojenčki cepljeni proti šestim nalezljivim boleznim ter prejmejo 5 odmerkov cepiv.*

Metode: *V retrospektivni raziskavi smo 279 dojenčkov razdelili v podskupine v skladu s programom cepljenja in vključili najpogostejše vzroke za umrljivost in število smrtnih primerov iz podatkovnega portala Nacionalnega inštituta za javno zdravje med leti 2007–2011.*

Rezultati: *Najpogostejši neposredni in posredni vzroki smrti dojenčkov so sindrom dihalne stiske (n = 22), skrajna nezrelost (n = 19), nekrotični*

Abstract

Purpose: *The infant mortality rate (IMR) is among the most important indicators of a nation's health and well–being. In Slovenia, over the last 55 years, infant mortality (IM) has decreased rapidly and vaccinations are undoubtedly the major contributing factor. In Slovenia, infant immunization is initiated at the age of 3 months. The vaccination schedule includes several doses of combined vaccines that should be administered according to the yearly program on immunization.*

Methods: *In this retrospective study, 279 infants were divided into subgroups in accordance with the vaccination program. The structure of the study design used the data of the National Institute of Public Health of Slovenia regarding the causes of IM for the years 2007–2011.*

Results: *Direct and indirect leading causes of death were infant respiratory distress syndrome (n = 22), extreme*

enterokolitis (n = 18), skrajno majhna porodna teža (n = 14) in sindrom hipoplastičnega levega srca (n = 14). Največja stopnja umrljivosti dojenčkov (85,30 %) velja še pred predpisanim programom obveznega cepljenja. V obdobju obveznega cepljenja (starost dojenčkov od 3 do 12 mesecev) je stopnja umrljivosti dojenčkov 14,70 %.

Zaključek: *Prezgodnji porod in zapleti, razvojne, prirojene nepravilnosti in genetske bolezni so glavni in najpogosteješi vzroki umrljivosti dojenčkov. Umrljivost je največja v prvih dveh mesecih življenja, še preden se prične program cepljenja dojenčkov. V obdobju obveznega cepljenja je smrtnost dojenčkov nizka, vzroki za smrt so prirojene ali genetske bolezni. Vzroki smrti in rezultati raziskave primerjalnih podskupin v obdobju obveznega cepljenja do enega leta starosti med leti 2007–2011 utemeljujejo, da cepivo ni vzrok za smrt dojenčkov.*

immaturity (n = 19), necrotizing enterocolitis (n = 18), extremely low birth weight (n = 14), and hypoplastic left heart syndrome (n = 14). The maximum IMR (85.30%) occurred before the recommended vaccination period. During the prescribed program of vaccination, the IMR was 14.70%.

Conclusion: *Genetic alterations, congenital abnormalities, and preterm birth complications are the major and leading causes of IM. Most instances of IM occur within the first two months of life, before the recommended vaccinations. During the recommended vaccination period, IM is low and causes of death are largely congenital and genetic diseases. The results of the comparative study during the recommended vaccination schedule by the end of the first year of life from 2007 to 2011 substantiates that the vaccines are not a major cause of IM.*

INTRODUCTION

Progress in achieving high vaccination coverage has significantly reduced morbidity and mortality caused by vaccine–preventable diseases (1,2). Immunization has proved to be highly effective for maintenance of public health by reducing mortality from communicable diseases, such as pneumonia, sepsis, and meningitis (3,4). Social and biomedical research has indicated that the infant mortality rate (IMR), i.e., the number of deaths among infants aged > one year per 1,000 live births in a single calendar year, is an important indicator of a nation's health and well–being. The IMR varies depending on social, demographical, ethnical, political, and environmental factors (5). In Slovenia, the IMR is relatively favorable when compared with developed countries. There are three main indicators of infant mortality (IM): the rate of stillbirths, perinatal mortality, and prematurity. The most common cause of IM in Slovenia is prematurity, accounting for at least half of infant deaths, primarily because of complications, such as infant respiratory distress syndrome (IRDS), brain hemorrhage, and infection, whereas one–third is due to congenital abnormalities, birth complications, and cancer (6).

The IMR in Slovenia is relatively low due to improved health care and prevention programs, which have resulted in a significant decrease in IM from 1960 to 2011 (Figure 1). A detailed analysis of the IMR in Slovenia showed that since the implementation of strategies for registration, prevention, and control, many communicable diseases, such as diphtheria and poliomyelitis, which represent serious threats to human health, have now been eliminated. Measles, mumps, and rubella (MMR) viruses have not been circulating for many years. The epidemiological status of measles from 1946 to 1960 in comparison with 1968, when vaccinations were first required, to 2011 has significantly improved, resulting in a decrease in the number of deaths to a rate of 0.2%. There has been impressive progress in reducing the incidences of mumps and rubella. The reduction in the number of infections of mumps was most obvious after the requirement for vaccination in 1979, which resulted in a decrease

in the number of new infections from an average of 655 per year to four. The reduction in rubella was most obvious after the requirement for vaccination in 1971, which resulted in a decrease in the number of new infections from an average of 7179 per year to none in 2011. In 2011, as compared to 1951, the number of deaths from tetanus has dramatically decreased (n = 3), as did the number of new infections (n = 2). Hence, the introduction of new vaccines will significantly reduce circulation of the causative agents of common communicable diseases, as shown with the varicella vaccine (7).

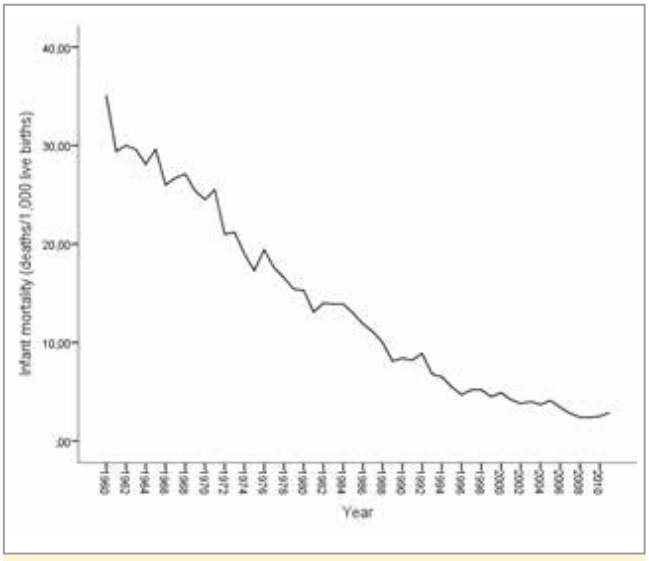

Figure 1. *IMR (deaths/1000 live births) in Slovenia from 1960 to 2011.*

In Slovenia, the immunization schedule for infants from birth to the end of the first year of life includes three doses of combined vaccines against diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenzae type b (Hib) to be administered by the end of the first year of life (preferably in months 3, 5, and 6). The first vaccination against DTP (diphtheria, tetanus and pertussis), Hib, and IPV (inactivated polio vaccine) should be administered at 3 months of age. Three doses of the DTP/Hib/IPV vaccine should be given by the end of the first year of age with revaccination one year after the third dose, and then revaccination of DTP at 8 years of age. The MMR vaccine should be given at 12–18 months of age, followed by a second dose at 5–6 years of age, before entering school.

METHODS

The aim of this retrospective cohort study was to investigate the influence of the expanded program on immunization in the first year of life on IM in Slovenia. To show the usefulness of these data in the context of protective benefits by vaccination, a hypothetical cohort of 279 infants was constructed by accepting the estimated rate as the true constant rate over the follow–up period. The study included 279 reports of infant death from 2007 to 2011 (55 infants in 2007, 52 each in 2008 and 2009, 56 in 2010, and 64 in 2011). The 279 infants were divided into subgroups in terms of vaccination eligibility by age (i.e., 0–2.99, 3–5.99, 6–8.99, and 9–12 months).

Morbidity and mortality data were analyzed to describe the basic features of the main diseases associated with IM. With the data portal of the National Institute of Public Health of Slovenia, The International Classification of Diseases (ICD–10 version), age classification of infants, and graphics analysis, the basis of quantitative data analysis was formed. Incorporating exact background rates of disease could strengthen vaccine safety assessment and provide evidence–based yearly populations.

The IMR of the cohort of infants that was divided into subgroups in terms of eligibility for vaccination according to the routine vaccination schedules, which start at 3 months of age. Those in the pre–vaccination period (before vaccine administration) were included for a comprehensive comparison of the IMR by the end of the first year of life.

The study participants were followed–up from the date of birth until the date of death due to the selected diagnoses described in Tables 1 and 2 in the years 2007 and 2011 in Slovenia. All study participants were subject to standard immunization through the vaccination program. All statistical analyses were conducted with SPSS statistical software (IBM–SPSS, Inc., Chicago, IL, USA).

RESULTS

To study IM in the period from 2007 to 2011, the cohort of infants was divided into groups in terms of the pre–vaccination period (before the age of 3 months) and the vaccination period (age >3 months to 12 months, when vaccines are given according to the routine vaccination schedule). To study the correlation between IM and the scheduled vaccination program in Slovenia, infants were divided into subgroups according to the prescribed immunization schedule for infants, which recommends three doses of DTP/Hib/IPV vaccine administered preferably in months 3, 5, and 6. According to the yearly immunization schedule, the infants were divided into subgroups according to age of vaccination (i.e., 3–5.99, 6–8.99, and 9–12 months). Some vaccines are known to cause uncommon and severe adverse effects, such as hypersensitivity reactions, fever, redness, swelling, soreness, and/or tenderness, which may result in effects similar to the disease symptoms shortly after vaccination, although no such correlation has been established. Analyses of the incidences of such adverse effects are published on the website of the National Institute of Public Health and are summarized in this article along with a partial review of yearly reports of cohort studies examining non–casual correlations between IM and vaccine usage in Slovenia.

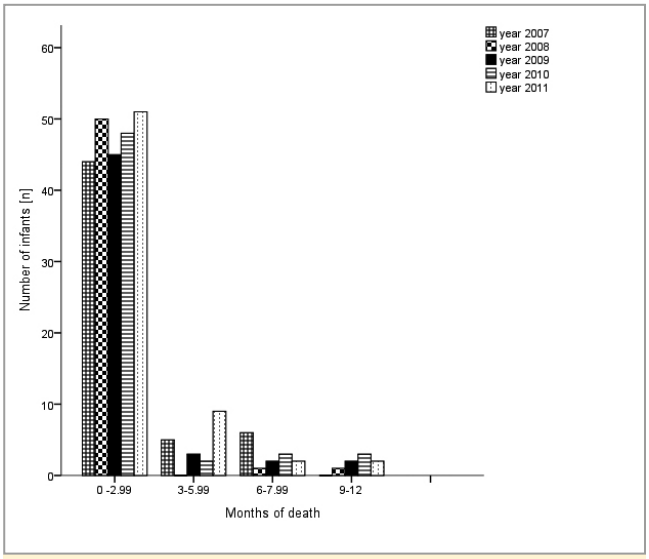

Figure 2. *Number of infant deaths by age at death from 2007 to 2011 in Slovenia.*

During the observation period, the majority of deaths occurred among infants aged >3 months. The data from 2007 to 2011 showed that the largest percentage (85.30%) of unvaccinated infants died at the age 0–2 months, while only 14.70% of vaccinated infants aged 3–12 months had died (Figure 3).

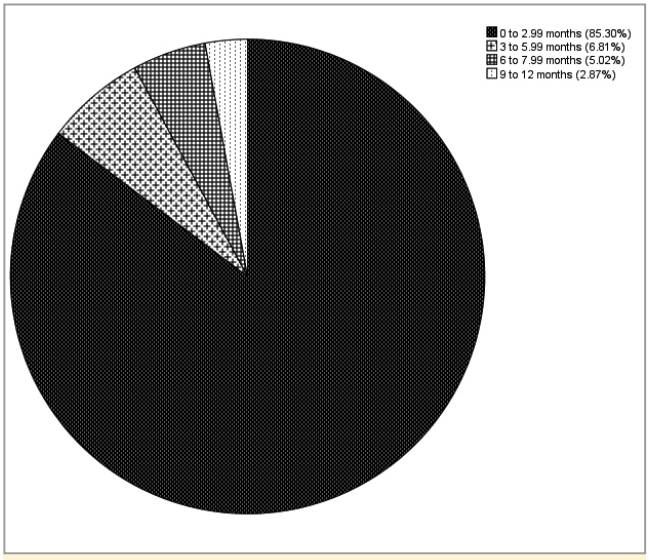

Figure 3. *Percentage of infant deaths according to age in Slovenia. Infants were divided into subgroups according to age in months and routine vaccination schedules during the period of 2007 to 2011.*

In the year 2007, 67.86% of infant deaths before the age of one month were most often because of intense birth asphyxia, sudden infant death syndrome (SIDS), IRDS, necrotizing enterocolitis, and congenital hernia. Meanwhile, 9.01% of infants aged 3–5.99 months died from bronchopneumonia, hypoplastic left heart syndrome, SIDS, and Down's syndrome (Figure 2, Table 2), and 10.91% of infants aged 6–8.99 months died from hemophagocytic lymphohistiocytosis, double outlet right ventricle, acute myelogenous leukemia, neurodegenerative disease (NDD), and Edward's syndrome (Figure 2, Table 2). The causes of death of a particular cohort of immunized children varied.

In the year 2008, 78.85% of infant deaths before the age of one month were most often caused by IRDS, extremely low birth weight, bacterial sepsis, undefined circumstances in the perinatal period, hypoplastic

left heart syndrome, and intracerebral hemorrhage. Meanwhile, 1.92% of infants aged 6–8.77 months died from bronchopulmonary dysplasia (Figure 2, Table 2) and 1.92% of infants aged 9–12 months died from a NDD (Figure 2, Table 2). The causes of death of a particular cohort of immunized children varied.
In the year 2009, 67.31% of infant deaths before the age of one month were most often caused by extremely low birth weight, intra–abdominal infection, deformations with brain reduction, extreme immaturity, difficult birth asphyxia, and primary atelectasis. Meanwhile, 5.77% of infants aged 3–5.99 months died from endocrine disorders, infantile spinal muscular atrophy, and other defined and unspecified causes of death (Figure 2, Table 2), 3.85% of infants aged 6–8.99 months died from congenital myasthenic syndrome and hypoplastic left heart syndrome (Figure 2, Table 2), and 3.85% of infants aged 9–12 months died from hemophagocytic lymphohistiocytosis and spinal muscular atrophy (Figure 2, Table 2). The causes of death of a particular cohort of immunized children varied.

In the year 2010, 71.43% of infant deaths before the age of one month were most frequently caused by extreme immaturity, undefined lung hemorrhage, undefined intraventricular hemorrhage, newborn jaundice, necrotizing enterocolitis, and SIDS. Meanwhile, 3.57% of infants aged 3–5.99 months died from spinal muscular atrophy and undefined intraventricular hemorrhage, 5.36% of infants aged 6–8.99 months died from necrotizing enterocolitis, congenital heart defects, and SIDS, and 5.36% of infants aged 9–12 months died from NDD, other defined and unspecified causes of death, and bronchopneumonia (Figure 2, Table 2). The causes of death of a particular cohort of immunized children varied.

In the year 2011, 82.81% of infant deaths within the first month of life were most often casued by extremely low birth weight, extreme immaturity, IRDS, sepsis caused by group B streptococcal infection, hypoplastic left heart syndrome, and SIDS. Meanwhile, 14.06% of infants aged 3–5.99 months died from Waterhouse–Friderichsen syndrome, necrotizing enterocolitis, coarctation of the aorta, Edward's syndrome, bronchopneumonia, a common atrial trunk, and other defined and unspecified causes of death (Figure 2, Table 2), 3.125% of infants aged 6–8.99 months died from NDD and malignant renal neoplasm (Figure 2, Table 2), and 3.125% of infants aged 9–12 months died from hemolytic–uremic syndrome and malnutrition (Figure 2, Table 2). The causes of death of a particular cohort of immunized children varied.

The principle causes of IM were related to NDD, extremely low birth weight, extreme immaturity, intense birth asphyxia, defined and undefined intraventricular hemorrhage, SIDS, and IRDS (Table 1). Although rarely, some diagnosis occurred only once during the observation period. The causes of death varied most at different ages of infants receiving vaccinations from immunization programs at three doses of DTP/Hib/IPV with an interval between doses from 2007 to 2011 (Table 2).

A391 = Waterhouse–Friderichsen syndrome; C640 = Malignant renal neoplasm; C920 = Acute myelogenous leukemia; D432 = Brain diseases; D593 = Hemolytic–uremic syndrome; D761 = Hemophagocytic lymphohistiocytosis; E348 = Endocrine (hormone) disorders; E410 = Malnutrition; G120 = Infantile spinal muscular atrophy; G129 = Spinal muscular atrophy; G319 = NDD; G702 = Congenital myasthenic syndromes; J159 = Bacterial pneumonia; J180 = Bronchopneumonia; P070 = Extremely low birth weight; P071 = Low birth weight; P072 = Extreme immaturity; P210 = Intense birth asphyxia; P220 = IRDS; P229 = Respiratory distress; P241 = Aspiration of amniotic fluid and mucus; P261 = Massive pulmonary hemorrhage; P269 = Undefined lung hemorrhage; P271 = Bronchopulmonary dysplasia; P280 = Primary atelectasis; P285 = Respiratory failure; P351 = Congenital cytomegalovirus infection; P369 = Bacterial sepsis; P392 = Intra–abdominal infection; P399 = Undefined infection, typical of the neonatal period; P523 = Undefined intraventricular hemorrhage; P522 = Intraventricular hemorrhage; P523 = Intraventricular hemorrhage (undefined); P524 = Intracerebral hemorrhage; P770 = Necrotizing enteroco-

Table 1. *Principal diagnoses associated with IM in Slovenia from 2007 to 2011.*

Year/International Classification of Diseases (ICD–10)*				
2007	**2008**	**2009**	**2010**	**2011**
D761		D761		
G319	G319		G319	G319
J159		J159		
J180			J180	
P070	P070	P070		P070
P072	P072	P072	P072	P072
P210	P210	P210	P210	P210
P285		P285	P285	
P369	P369	P369		
P399			P399	P399
P522	P522	P522	P522	
P770	P770	P770	P770	P770
Q234	Q234	Q234	Q234	Q234
Q249			Q249	
Q606				Q606
Q897	Q897		Q897	
R950		R950	R950	R950
	P220	P220	P220	P220
	P241	P241		
	P269		P269	
	P280	P280		P280
	P351	P351		
	P392	P392	P392	
	P523		P523	P523
	P524		P524	
	Q049	Q049		
	Q251			Q251
		G129	G129	
		P229		P229
		P261	P261	
		P832		P832
		Q043		Q043
		Q200		Q200
		Q913		Q913
		R990	R990	R990
			P071	P071

**ICD–10*

litis; P832 = Hydrops (not due to hemolytic disease); R950 = SIDS; R990 = Other defined and unspecified causes of death; P969 = Undefined circumstances in the perinatal period; Q043 = Other deformations with brain reduction; Q049 = Congenital brain malformation; Q200 = A common atrial trunk; Q201 = Double outlet right ventricle; Q248 = Multiple innate malformations; Q249 = Congenital heart defects; Q251 = Coarctation of the aorta; Q234 = Hypoplastic left heart syndrome; Q606 = Potter's syndrome; Q897 = Multiple congenital malformations; Q909 = Down's syndrome; and Q913 = Edward's syndrome.

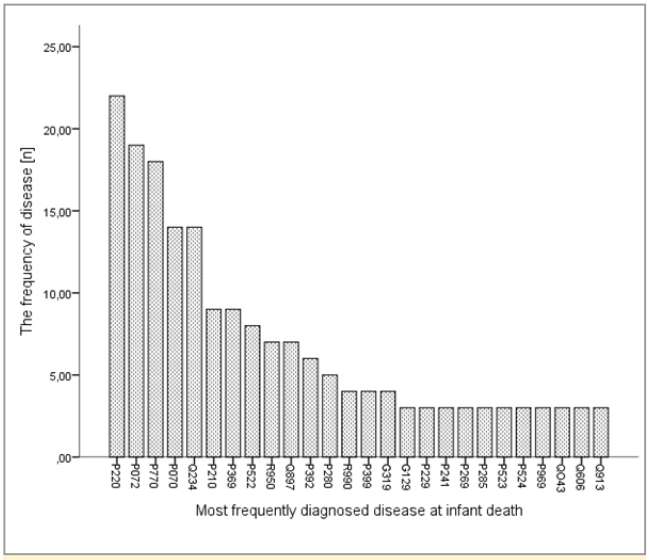

Figure 4. *Frequencies of principal diagnoses associated with IM in Slovenia that occurred more than once by the end of the first year of life from 2007 to 2011.*

Frequency analysis showed that infant deaths occurred mainly in the first month of life or immediately after birth, when no intervention with vaccinations was in place (Figure 4). The results indicated that the most frequent and leading causes of IM were IRDS (n = 22), extreme immaturity (n = 19), necrotizing enterocolitis (n = 18), extremely low birth weight (n = 14), hypoplastic left heart syndrome (n = 14), intense birth asphyxia (n = 9), bacterial sepsis (n = 9), intraventricular hemorrhage (n = 8), SIDS (n = 7), multiple congenital malformations (n = 7), intra–abdominal infection (n = 6), primary atelectasis (n = 5), other undefined and unspecified causes of death (n = 3), undefined infection

Table 2. *Diagnoses associated with IM in Slovenia among subgroups of infants immunized from 2007 to 2011.*

	Subgroup/International classification of Disease (ICD-10)*		
Year	3–5.99 months	6–7.99 months	9–12 months
2007	J180 (n = 1)	C920 (n = 1)	
	R950 (n = 2)	D761 (n = 1)	
	Q234 (n = 1)	G319 (n = 1)	
	Q909 (n = 1)	Q201 (n = 1)	
		Q913 (n = 1)	
2008		P271 (n = 1)	G319 (n = 1)
2009	E348 (n = 1)	G702 (n = 1)	D761 (n = 1)
	G120 (n = 1)	Q234 (n = 1)	G129 (n = 1)
	R990 (n = 1)		
2010	G129 (n = 1)	P770 (n = 1)	J180 (n = 1)
	P523 (n = 1)	R950 (n = 1)	G319 (n = 1)
		Q249 (n = 1)	R990 (n = 1)
2011	A391 (n = 1)	C640 (n = 1)	D593 (n = 1)
	J181 (n = 1)	G319 (n = 1)	E410 (n = 1)
	P770 (n = 2)		
	Q200 (n = 1)		
	Q251 (n = 1)		
	Q913 (n = 1)		
	R990 (n = 2)		

(n = 3), NDD (n = 3), spinal muscular atrophy (n = 2), respiratory distress (n = 2), aspiration of amniotic fluid and mucus (n = 2), undefined lung hemorrhage (n = 2), respiratory failure (n = 2), undefined intraventricular hemorrhage (n = 2), intracerebral hemorrhage (n = 2), undefined circumstances in perinatal period (n = 2), other deformations with brain reduction (n = 2), Potter's syndrome (n = 2), and Edward's syndrome (n = 2).

Correlation analyses showed that the most frequent causes of death in the subgroups of infants that were eligible to receive vaccines according to the recommended vaccination schedule were NDD (n = 4), other undefined and unspecified causes of death (n = 4), spinal muscular atrophy (n = 2), undefined intraventricular hemorrhage (n = 1), other deformations with brain reduction (n = 1), and Edward's syndrome (n = 2).

The results of this study demonstrated that infant morbidity was more common due to one of these diseases than by DTP/Hib/IPV vaccination. There was no correlation between vaccination and cause of death in infants in this retrospective study.

DISCUSSION

The causes of IM identified in this retrospective analysis were retrieved from a review of publications of anti–vaccination media, anti–vaccination group websites, internet forums, and some published articles consisting of incorrect, non–proven, and non–evidence–based arguments about the dangers and doubts about the safety of vaccines (8–14).

Death may occur suddenly with no defined cause in some cases (5,15). Mortality is often dependent on genetic, environmental, social, and economic factors (16). Genetic alterations, congenital abnormalities, and preterm birth complications are leading causes of death in infants, as verified by the present study. Necrotizing enterocolitis

is a devastating and common acute gastrointestinal disease in infants of very low birth weight, with a mortality rate ranging from 10% to 50% (17, 18). IRDS is a serious respiratory disease in infants, while congenital brain and spinal cord malformations, as well as malformations of the central nervous system arise during the second, third, and fourth weeks of human embryogenesis (19, 20). Intraventricular hemorrhage is a complex disorder due to both environmental and genetic factors that occur during the critical period before gestational week 32 or 33 (21). Hypoplastic left heart syndrome with a highly restrictive or intact atrial septum is associated with a very high mortality rate (22). Spinal muscular atrophy is a rare autosomal recessive disease with devastating neurodegenerative consequences and is the most common genetic cause of IM (23, 24).

This study provides a summary of IM data among 279 infants by the end of the first year of life during the period of 2007 to 2011. A great majority of infant deaths (70.60%) occurred in the first month of life before vaccination and an additional 14.70% of infants died between the ages of 3 and 12 months after receiving vaccinations. The leading causes of death, particularly in premature infants, were IRDS, extreme immaturity, necrotizing enterocolitis, extremely low birth weight, and hypoplastic left heart syndrome. Genetic mutations and congenital abnormalities were among the most prominent causes of death of infants aged 3–12 months. NDD, other deformations with brain reduction, Edward's syndrome, spinal muscular atrophy, and undefined intraventricular hemorrhage are complex disorders associated with very high mortality rates. The diseases that are leading causes of IM predominantly occur independently of vaccination. The results of this study supports Shann's theory of the impossible long–term vaccine effects on diseases and death, and overrules the arguments about the toxicity of infant vaccines and the influence of the number of doses on infant morbidity and mortality (3, 4, 25–26).

It has been proven that immunization is a safe and effective form of control and elimination of life–threatening communicable diseases (5,27,28). IMR in low and middle income countries are still unacceptably high, which is largely attributable to the poor quality of general healthcare in developing countries (29). Statistical analysis identified that almost half of the deaths of children younger than 5 years occur in India, Nigeria, Democratic Republic of the Congo, Pakistan, and China (30). Non–communicable causes, pneumonia, preterm birth complications, and cardiac and infectious diseases are consistently attributed as the leading causes in various countries. Mortality surveillance is not reciprocal and the mortality rate is often correlated with race, ethnicity, geographic, environmental, and genetic factors, educational status, economic factors, age, and gender (5, 30, 31).

The results of this retrospective investigation from 2007 to 2011 in Slovenia showed a significantly lower frequency of deaths in the subgroup of vaccinated infants. However, these data do not indicate a causal relationship between vaccine and infant death or possible long–term effects of DTP/Hib/IPV. Hence, an infant is far more likely to be seriously injured by one of these diseases than by any recommended vaccine (Table 1, Table 2).

CONCLUSIONS

Vaccination of infants, children, adolescents, and adults has largely prevented the occurrence of vaccine–preventable diseases in Slovenia. IM in the years 2007–2011 primarily resulted from severe congenital anomalies, infectious, environmental, and genetic anomalies, or preterm birth. IMRs demonstrate the healthy effect of a vaccine with positive associations for vaccinations given before one year of age. The mortality of infants aged between 3 and 12 months was not associated with vaccination. However, further data collection and analysis are necessary at each phase of the recommended immunization schedules. Analysis of mortality data according to these vaccination schedules adds substantial insights and details needed to study the effects of vaccines and mortality of infants of various age groups.

Conflict of interest

The authors declare that no conflicts of interest exist.

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